5. rejected claims 7-11, 14-18 and 28-34 under 35 U.S.C. section 112, first paragraph.

6. rejected claims 28-34 under 35 U.S.C. section 112, second paragraph.

Applicant responds to the Office Action as follows.

II. Claim Amendments and Cancellations

Claims 7, 9, 15, 16 and 17 have been amended. Applicant hereby cancels claims 8, 11, 14, 18 and 28-34 without prejudice to further prosecution at a later date. Claims 37-38 have been added. The claims now pending are therefore claims clams 7, 9, 10, 15-17 and 37-38.

The addition of the word "bradycardia" to claim 7 is supported by at least original claim 18. The addition of the phrase "intrapericardial injection" to claim 7 to claim 7 is supported by at least original claim 8. The addition of the phrase "botulinum toxin" to claims 7, 9, and 15-17 is supported by at least original claim 11. Adding the word "type" to claims 15 and 16 is a minor clarifying amendment since "botulinum toxin A" is properly referred to (as in the amendment) as "botulinum toxin type A."

New claim 37 is supported by at least the specification at page 22, lines 1-3. New claim 38 is supported by at least claim 7 and by the specification at page 22, lines 2-3.

No new matter or new issues are raised by the claim amendments or by the added claims.

III. Resubmitted Information Disclosure Statement

Applicant resubmits herein the Supplemental Information Disclosure Statement which was mailed to the patent office on December 27, 2000, with an explanation of the relevance of the one non-English art item included with the IDS. The examiner is therefore asked to consider the relevance of the art submitted with the IDS and to return to the applicant with the next office action an initialed copy of the form PTO-1449.

IV. Amended Title

The title is amended from "METHOD FOR TREATING CARDIAC MUSCLE DISORDERS" to:

"METHOD FOR TREATING CARDIAC MUSCLE DISORDERS BY ADMINISTRATION OF A BOTULINUM TOXIN"

Applicant does not believe that it is appropriate to restrict the title to a "Botulinum Toxin type A" because:

> "The botulinum toxins comprise a family of pharmacologically similar toxins that block acetylcholine release from peripheral nerves and cause a flaccid paralysis. All of the serotypes of toxin can poison humans and other animals..."

(page 81, left hand side of Schantz, E.J., et al, *Properties and use of Botulinum toxin and Other Microbial Neurotoxins in Medicine*, Microbiol Rev. 56;80-

99:1992) (copy previously provided). Hence use of all the botulinum toxins, and not just botulinum toxin type A, is enabled by the specification.

V. Objection to Claim 8

Claim 8 has been cancelled. Hence, the objection to claim 8 should be withdrawn.

VI. Rejection of Claims 7-11, 14-18 and 28-34

The Office Action rejected claims 7-11, 14-18 and 28-34 under 35 U.S.C. section 112, first paragraph on the basis that these claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Thus, page 5 of the Office Action states that because the specification lacks any working examples, does not teach the time period in which the toxin should be administered or for how long or what specific doses of a botulinum toxin should be administered and that therefore the claims are not enabled by the specification.

Additionally, page 6 of the Office Action notes that the Lamanna (1988) reference state that botulinum toxin type A causes bradycardia, so that it is therefore not clear why one would want to use a botulinum toxin to treat bradycardia (as in the present claims) since Lamanna reports that botulinum toxin can cause bradycardia.

As summarized on page 6 of the Office Action, the claims are rejected under 112(1) due to "the large quantity of experimentation necessary to determine the dosage and safety of botulinum toxin, the route of administration in a subject, and the timing and duration of administration, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the art (see Johnson and Lamanna et al.), the unpredictability of the effects of botulinum toxin A on a subject (see discussion and recited references), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope."

Respectfully, the rejection is in error and should be withdrawn, for at least the following reasons:

A. *The Longhurst Declaration*: enclosed is a declaration from Dr. John Longhurst, an expert in the filed of cardiovascular medicine and the treatment of cardiac disorders such as bradycardia (see paragraph 5. of the Longhurst declaration). After carefully and thoroughly reading the present patent application it is Dr. Longhurst's opinion that "...this patent application provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient (i.e. in the presence of a pericardial effusion of sufficient magnitude to allow access to the pericardial space) to thereby increase the heart rate of a patient with symptomatic bradycardia." (paragraph 6 of the Longhurst declaration).

Dr. Longhurst further states in paragraph 7. of his declaration that "...in my opinion matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and

disease severity which factors are routine considerations determined on a patient by patient basis by a cardiologist of ordinary skill who has knowledge of the therapeutic use of a botulinum toxin."

Thus, the Longhurst declaration presents admissible expert opinion evidence which rebuts the *prima facie* case of lack of enablement made by the Office Action and the rejection of the claims under section 112(1) should therefore be withdrawn.

B. Additionally, please note that botulinum toxin has been used therapeutically in many thousands of humans since about 1978 in clinical settings to safety and effectively treat many different target tissues besides spastic or dystonic muscles, including, for example, conditions such as pain, inflammatory disorders, excessive sweating, achalasia, anal fissure, and headache[1] and it is known that the dose of toxin to use by local administration generally corresponds to the mass of tissue to be treated (see specification at page 25, lines 6-13). See also U.S. patents 6,306,403 (intracranial botulinum toxin), 6,265,379 (treatment of otic disorders with a botulinum toxin), 6,139,845 (cancer treatment with a botulinum toxin), and 6,261,572 (treatment of pancreatic disorders with a botulinum toxin)

Thus, it is incorrect to state that botulinum toxin has been "only been effective in the treatment of involuntary muscle contraction disorders, dystonia, and spasticity or segmental muscle regions" (page 5 of the Office Action). Note that the Johnson reference states at page 565 that botulinum toxin "has been effective in treatment of a myriad of disorders", including those recited by the

[1] See e.g. Borodic GE et al., *Botulinum toxin therapy for pain and inflammatory disorders: mechanisms and therapeutic effects*, Exp Opin Invest Drugs 2001; 10(8):1531-1544 (abstract enclosed); Silberstein SD., *Review of botulinum toxin type A and its clinical applications to migraine headache*, Expert Opin Pharmacother 2001; 2(1):1649-1654 (abstract enclosed); Glogau RG., *Treatment of palmar hyperhydrosis with botulinum toxin*, Semin Cutan Med Surg 2001 Jun; 20(2):101-108 (abstract enclosed), and Munchau A., et al., *Uses of botulinum toxin injection in medicine today. Regular review*, Br Med J 2000 Jan 15; 320 (7228): 161-165 (abstract enclosed).

Office Action. Even if it were correct that botulinum toxin has been used only to treat cholinergicly innervated muscles, note that the heart is a muscle (cardiac muscle) and the vagal nerve provides cholinergic innervation to the heart.

C. All claims in the present application are limited to a method for treating bradycardia by intrapericardial injection of a botulinum toxin to a cardiac muscle. Significantly, Example 2 at pages 31-33 of the specification discloses four methods for accessing the pericardial space for intrapericardial administration of a botulinum toxin to treat bradycardia. Additionally, it is important to note that the prior art teaches intrapericardial administration of various drugs to humans[2]. Thus, intrapericardial administration of a particular pharmaceutical (i.e. botulinum toxin) does not pose any undue or unknown technical difficulties.

D. With regard to the Lamanna (1988) article cited by the Office Action, please note that the present claims are directed to *in vivo* administration of a botulinum toxin directly into the pericardial space. Contrarily, Lamanna discloses only: (a) administration of a botulinum toxin systemically (i.e. by intravenous injection - see e.g. page71, end of the first paragraph of Lamanna), and; (b) administration of a botulinum toxin to an isolated (i.e. dennervated) heart. (see also page 71 of Lamanna). Thus, Lamanna does not disclose or suggest intrapericardial (i.e. local) administration of a botulinum toxin.

Intrapericardial administration of a botulinum toxin according to the present invention is carried out so as to avoid entry of the botulinum toxin into the systemic circulation (see e.g. page 25, lines 2-5 of the present specification). Systemic administration of significant amount of a botulinum toxin can be

---

[2] See e.g. Lerner-Tung MB., et al., *Pharmacokinetics of intrapericardial administration of 5-fluorouracil*, Cancer Chemother Pharmacol 1997; 40(4):318-320 (abstract enclosed); Tomkowski WZ., et al., *Intrapericardial cisplatin for the management of patients with large malignant pericardial effusion in the course of lung cancer*, Lung Cancer 1997 Mar; 16(2-3):215-222 (abstract enclosed), and; Maisch B., et al., *Intrapericardial treatment of inflammatory and neoplastic pericarditis guided by pericardioscopy and epicardial biopsy – results from a pilot study*, Clin Cardiol 1999 Jan; 22(1 Suppl 1): 117-22 (abstract enclosed)

expected to be very harmful or fatal in humans – the therapeutic uses of a botulinum toxin are all by local administration (i.e. subcutaneous, intramuscular or intraglandular), not by any systemic (i.e., intravenous) route. It is for this reason that the present claims are all directed to a particular local administration route for the toxin – by an intrapericardial route (i.e. into the pericardial sac which surrounds the heart).

Additionally, Lamanna's administration of a botulinum toxin to an isolated heart also has no relevance to the claimed invention. Applicant's specification at page 1, lines 15-16, page 24, lines 7-18 and at page 25, lines 3-5 discloses that the vagus (parasympathetic) nerve innervates the heart, and that bradycardia can be treated by the action of a botulinum toxin upon the vagal ending in the heart without entry of the botulinum toxin into the systemic circulation. Note as set forth at page 1, lines 17-18 of the specification that "Heart rate can be increased by sympathetic stimulation and decreased by vagal stimulation." Thus, a proposed mechanism for the efficacy of the present claimed invention is inhibition of vagal (parasympathetic, cholinergic) activity by intrapericardial (direct, local) administration of a botulinum toxin. Down regulation of vagal activity thereby permit the unaffected sympathetic (adrenergic) innervation of the heart to reduce or eliminate the bradycardia. The isolated heart preparation of Lamanna is a denervated heart.

Hence, both the systemic toxin administration (strongly contraindicated in humans – since this would cause botulism)) and the "vagotomy" (isolated) heart preparation used by Lamanna have no applicability to the present invention. Hence, the observations in the Lamanna reference are of little or no relevance to the present claimed invention.

For these reasons the section 112(1) rejection of claims 7-11, 14-18 and 28-34, as amended, should be withdrawn.